Diagnóstico genético y Medicina Personalizada

Manuel Pérez Alonso

Instituto de Medicina Genómica

Parque Científico de la Universidad de Valencia

www.imegen.es

INDICE

- Los genes y el genoma
- Las enfermedades genéticas
- El diagnóstico genético
- Medicina Genómica y Medicina Personalizada
- El Instituto de Medicina Genómica
- Dónde seguir informados

Los genes y el genoma

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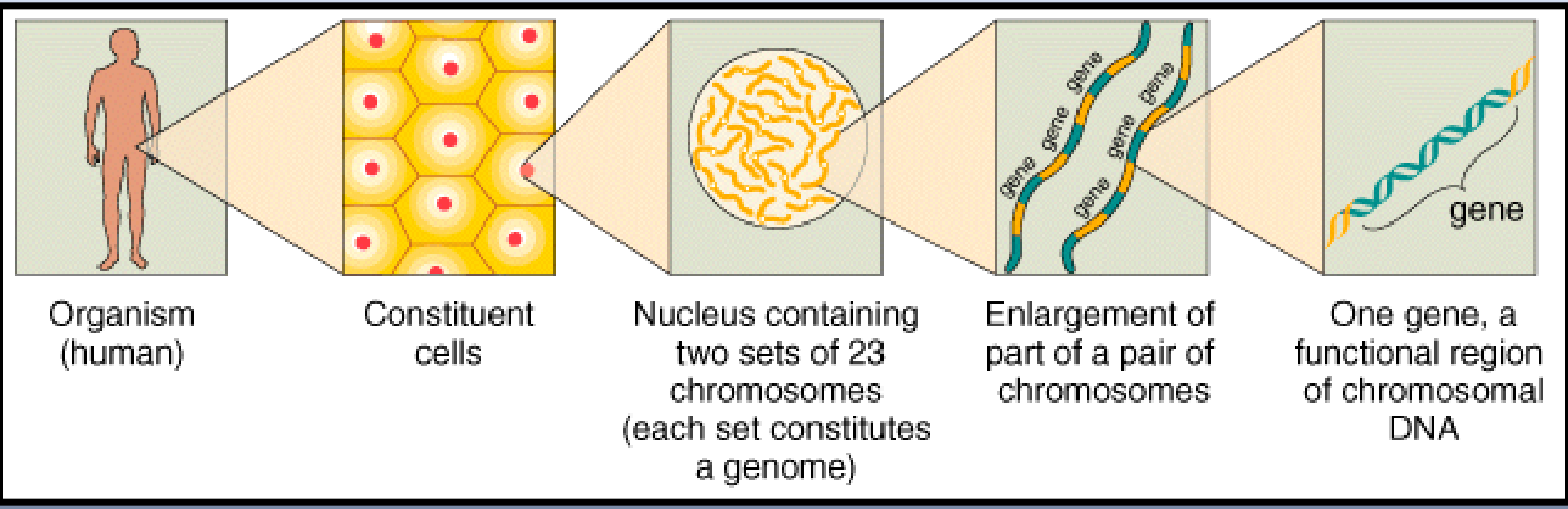
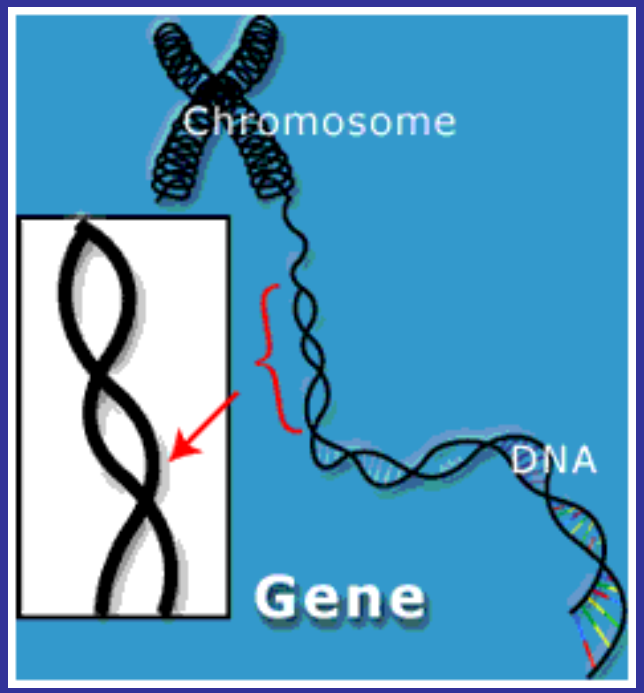
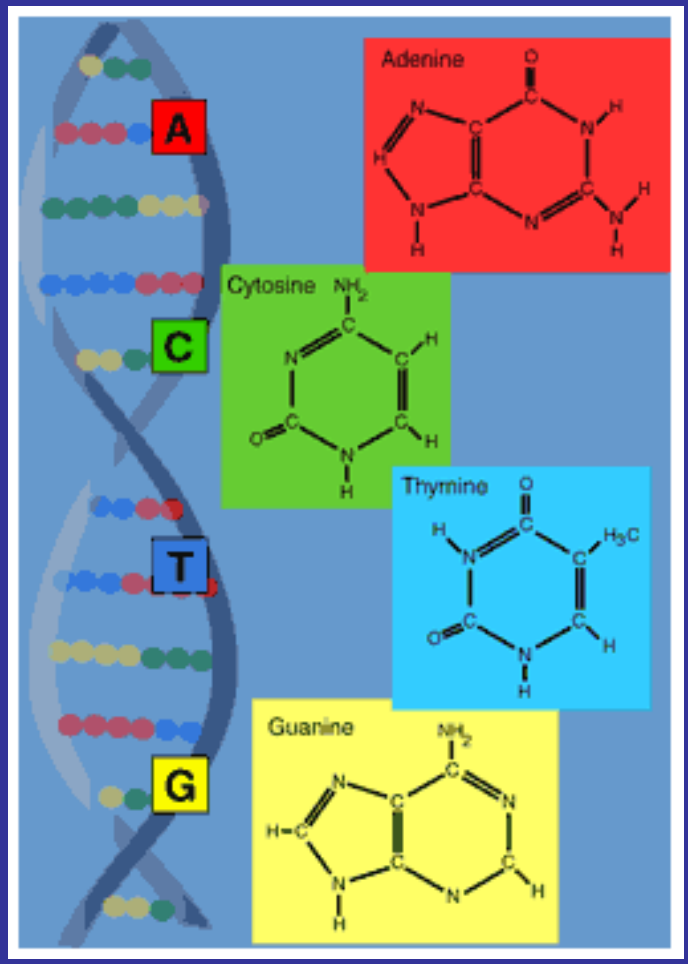
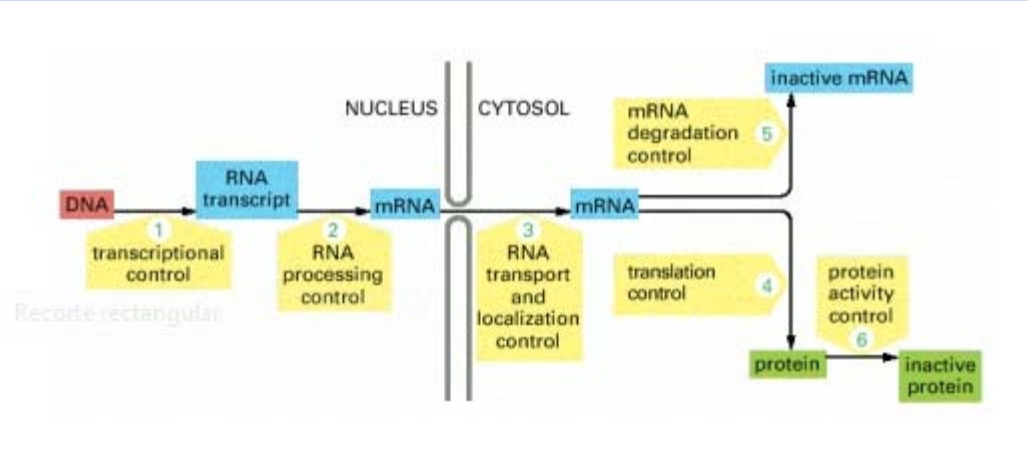
Dos genomas en cada célula



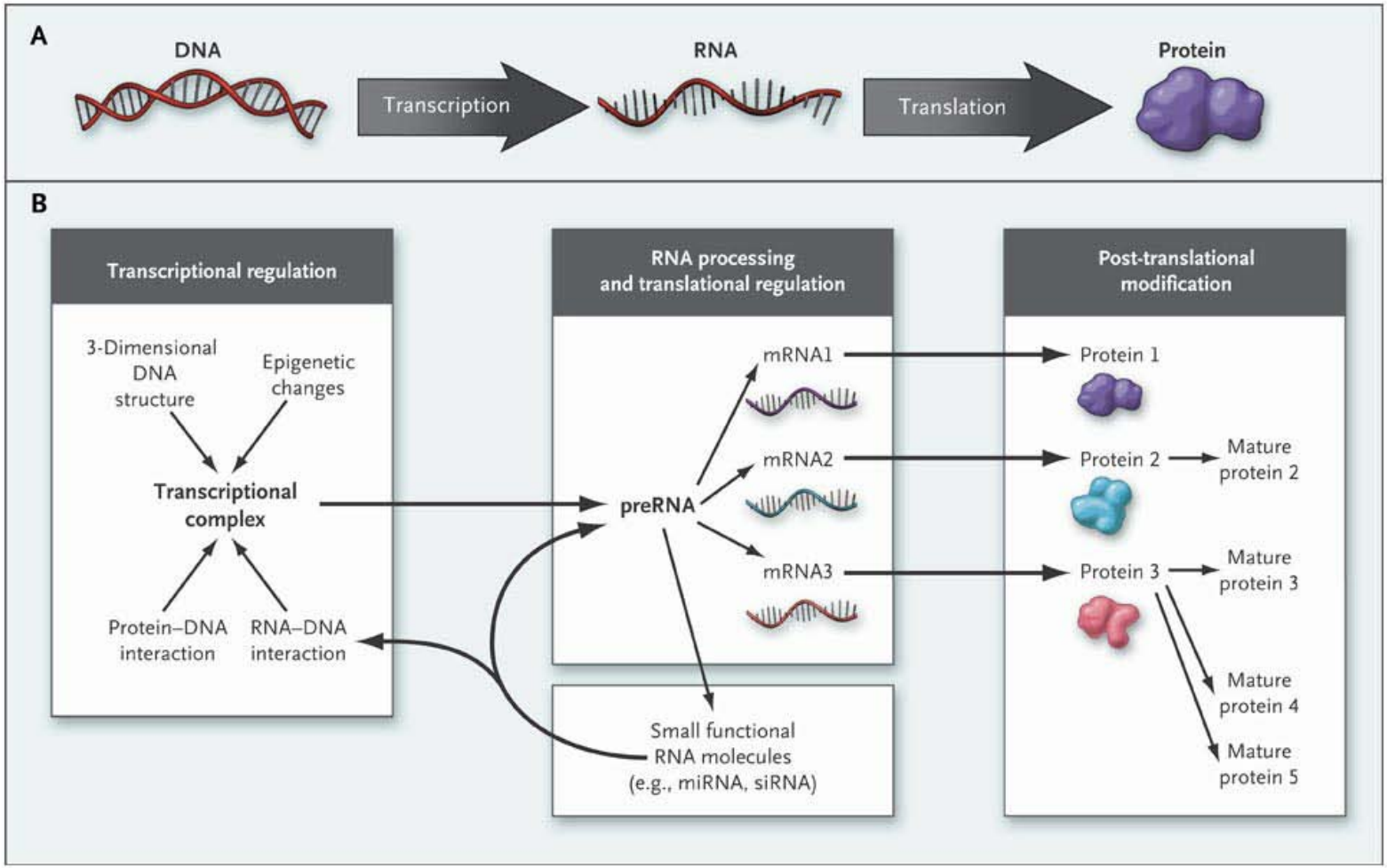

Chromosome
DNA
Gene


A
C
T
G
Adenine
Cytosine
Thymine
Guanine

Dogma Central de la Biología Molecular



Dogma Central expandido



Feero et al (2010). N Engl J Med 362: 2001-2011.

El genoma es una biblioteca

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GAATTCGCCGGTTAGGTTTTAGTATCAAGAAGAGAAGGAAATTTTGGACAGTGAATGGGC
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ATATGCGTGAAAGTCTTTAAATGCGTTTTTCCTTTTTCTTCACCATAAACCTTCTAGTTC
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ATTGCATCCAAGAATGAATTAACTTTTACTAGGCCAGAAGTGTAGCTAACATAGAAGAGG
CCCATTATAAAACTCTTTAAAATCAAAATCTAAAACAGGCCCAGCCCATTCATAACAAAG
CCCTAATATATCGAGTAAACCTAGCTCCACTCAAAACCTAACTATATAACCTTCACACAC
ACTCATAACCTCTTCCTCATCCCCTTAAAAAACCCTAAGAGTAGAGACTCTCTCAATCCC
GGCGGCGAAGATGAAGTACAACCCAAGAGTGACCTCTTCTCGCAGAAAGAACAGGAAGGC

NCBI

NCBI Map Viewer

PubMed | Nucleotide | Protein | Genome | Gene | Structure | PopSet | Taxonomy | Help

Search for [ ] on chromosome(s) [ ] assembly [All] Find Advanced Search

Map Viewer
- Map Viewer Home
- Map Viewer Help
- Human Maps Help
- Release Notes

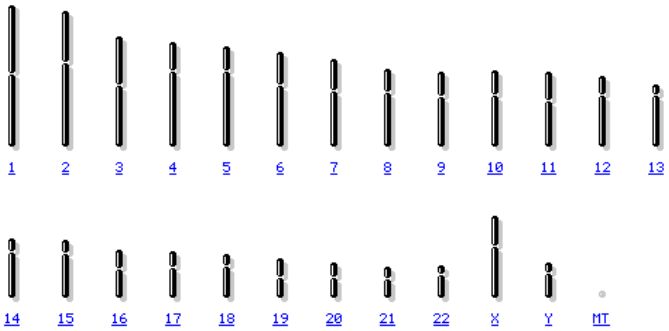
NCBI Resources
- Genome Project
- Trace Archive (Venter)
- RefSeq
- Whole Genome Association (WGA)
- Human Genome Resources
- GRC
- Consensus CoDing Sequence (CCDS)
- Trace FTP (Personal Genomics)
- NCBI Handbook
- Trace Archive (Watson)

Organism Data in GenBank
- EST
- Genomic

Homo sapiens (human) genome view

Build 37.2 statistics Switch to previous build

BLAST search the human genome



Lineage: Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo; Homo sapiens

November 2010: NCBI released an incremental update of the human genome reference assembly and updated annotation for all assemblies. The chromosomes and alternate loci regions are not changed; the new assembly includes the second set of genomic region Patches released by the Genome Reference Consortium (Genome Reference Consortium (GRC)) and is named GRCh37.p2. A previous version of the reference genome assembly, NCBI Build 36.3, can still be accessed for Map Viewer display and for BLAST. For additional information about changes, statistics, and the status of the CCDS project please refer to:

- Release Notes
- Statistics
- CCDS Project

The NCBI Map Viewer provides graphical displays of features on the human genome sequence assembly as well as cytogenetic, genetic, physical, and radiation hybrid maps. Extensive documentation is provided to describe the resource features and methods used, tutorials, and statistics.

Map features that can be seen along the sequence include genes, transcripts, NCBI contigs (the 'Contig' map), the BAC tiling path (the 'Component' map), STSs, FISH mapped clones, ESTs and transcripts from several different organisms, Gnomon predicted gene models, and more.

www.ncbi.nlm.nih.gov/genome/guide/human

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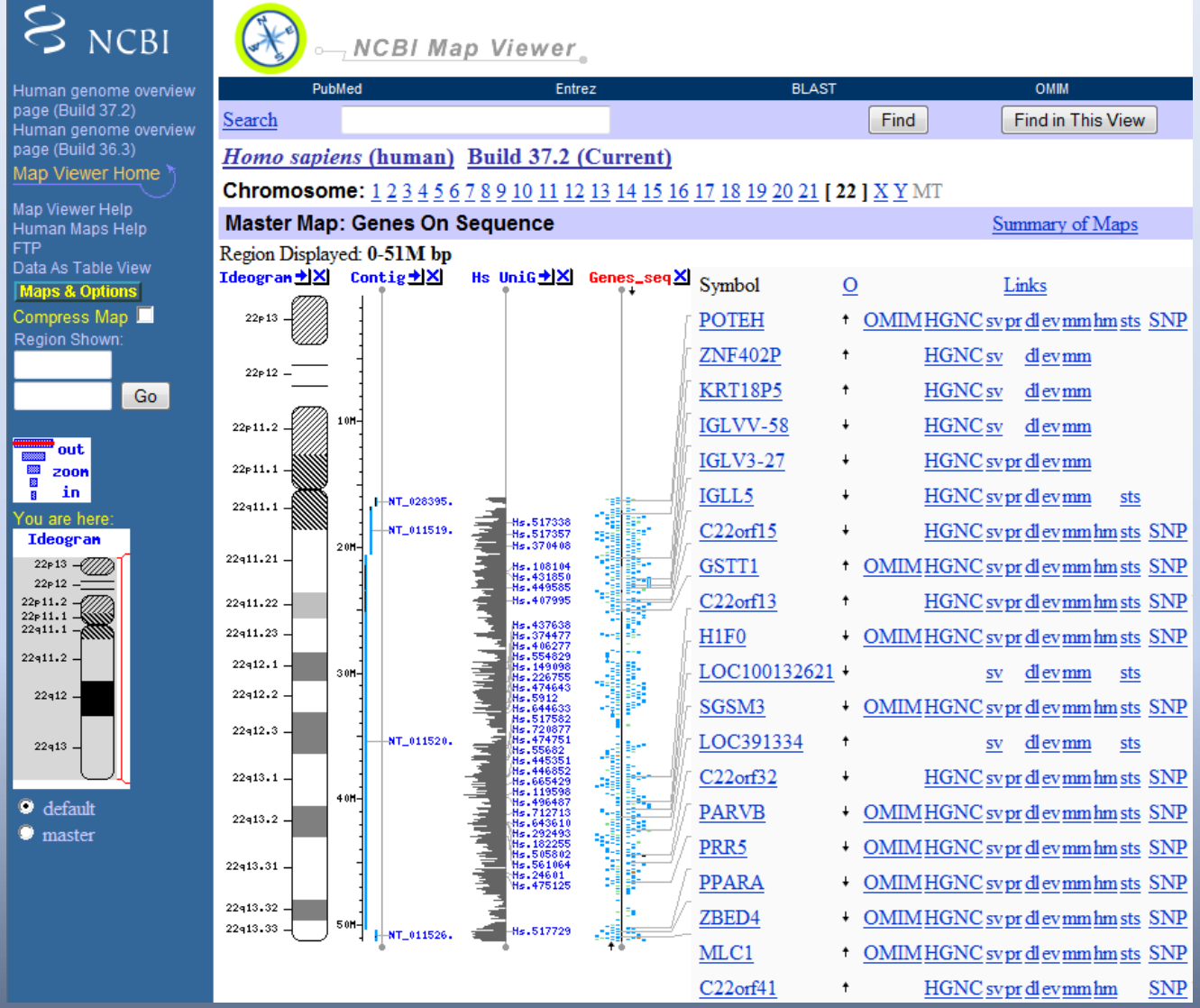

www.ncbi.nlm.nih.gov/genome/guide/human

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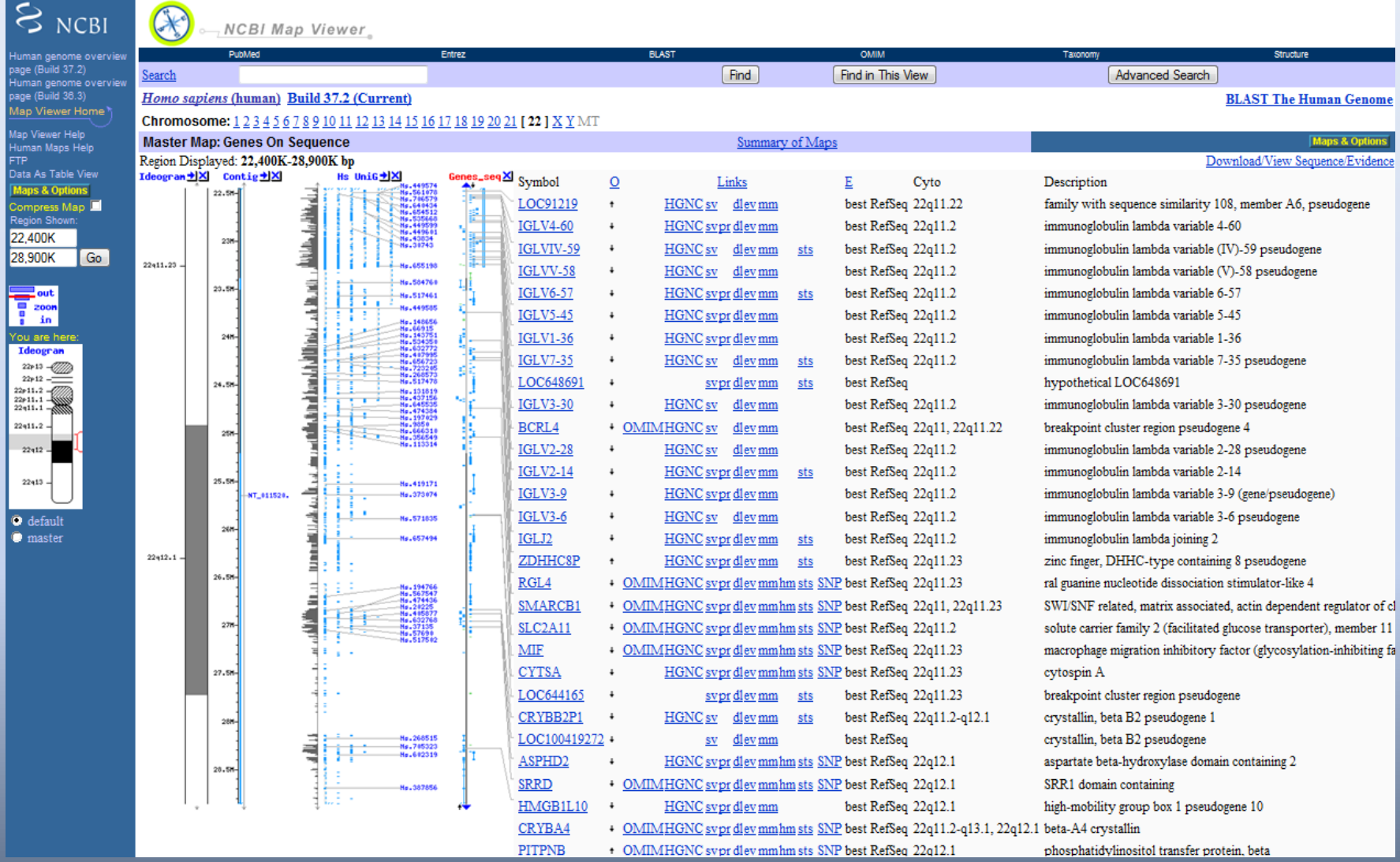

www.ncbi.nlm.nih.gov/genome/guide/human

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El tamaño del genoma humano

3.000 millones de pb = 3 Gb

30.000 genes, aprox.

Las enfermedades genéticas

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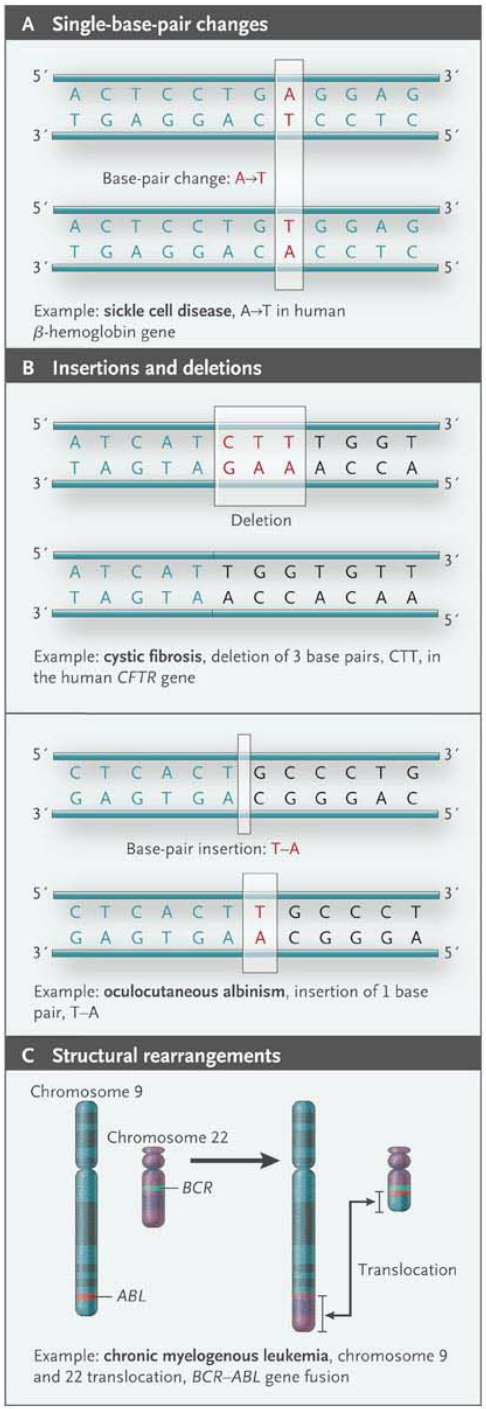

Mutaciones del genoma humano

Feero et al (2010). N Engl J Med 362: 2001-2011.

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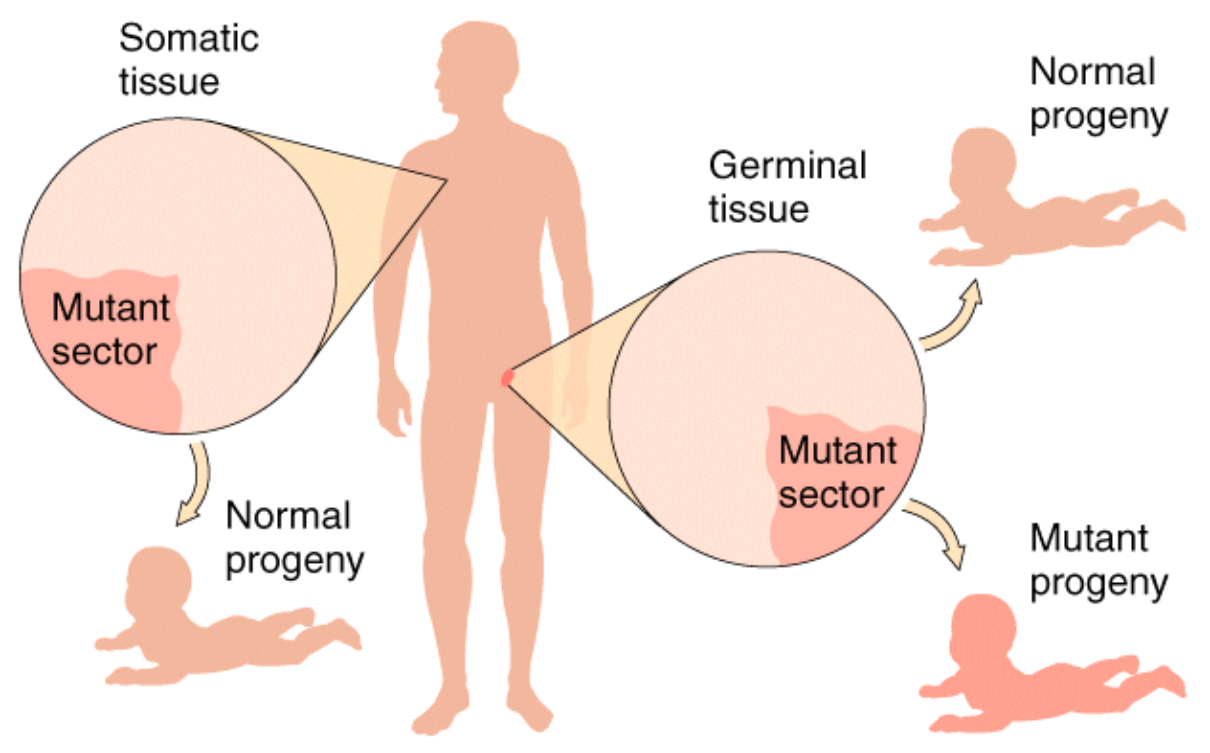
Mutaciones heredables y mutaciones no heredables

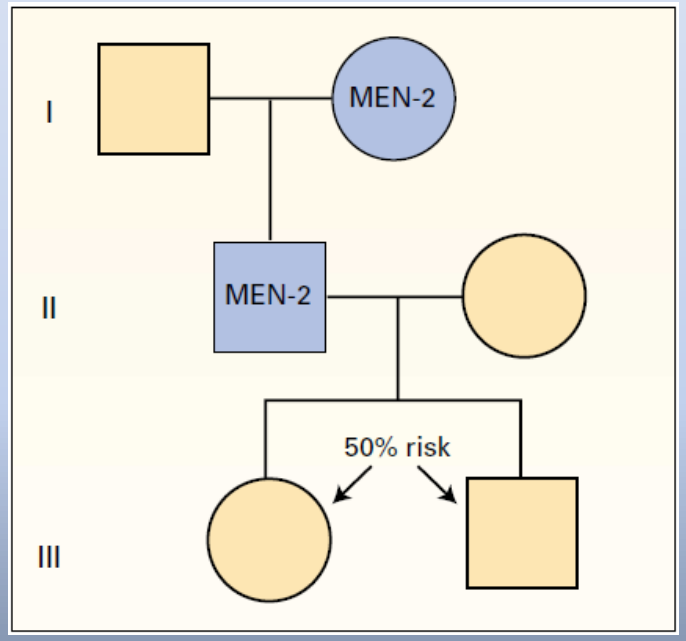


Dos tipos de herencia

- **Herencia mendeliana simple**: son enfermedades monogénicas (casi siempre enfermedades raras).

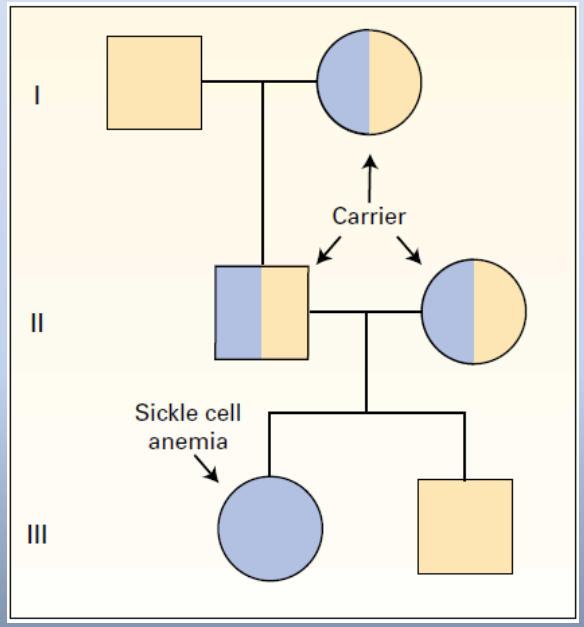
- **Herencia compleja**: son enfermedades multifactoriales (casi siempre enfermedades comunes, aunque algunas son enfermedades raras).

Herencia autosómica dominante



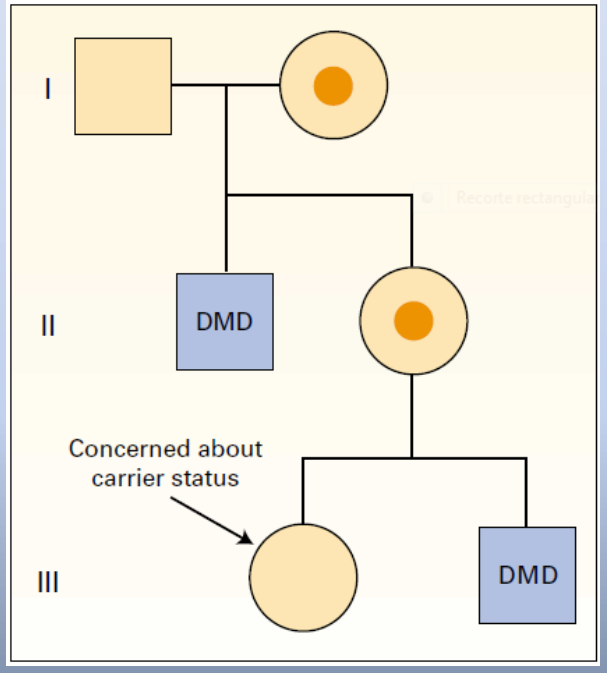
(Ej. Neoplasia endocrina múltiple)

Herencia autosómica recesiva



(Ej. Anemia falciforme)

Herencia recesiva ligada al X



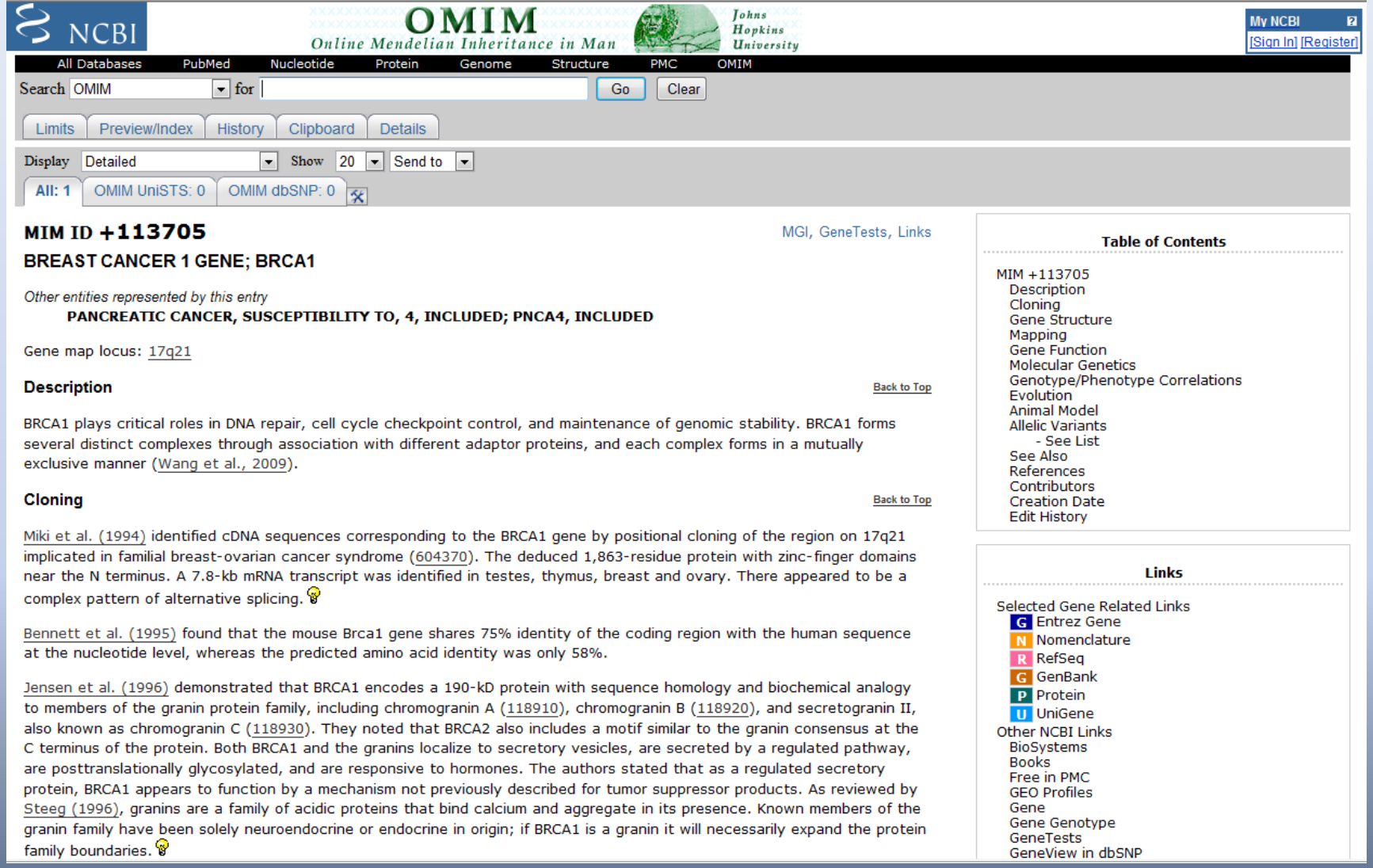
(Ej. Distrofia muscular de Duchenne

Ejemplos de enfermedades genéticas

Fibrosis quística
Hemofilia
Síndrome de Marfan
Talasemia
Poliquistosis renal
Distrofia miotónica
Retinitis pigmentosa
Ataxias hereditarias
Síndrome de Prader-Willi
Cáncer de mama y ovario
Osteogénesis imperfecta

Distrofia muscular de Duchenne
Enfermedad de Huntington
Neurofibromatosis
Enfermedad de Charcot-Marie-Tooth
Fenilcetonuria
Síndrome del X-frágil
Acondroplasia (enanismo)
Hemocromatosis
Hipercolesterolemia familiar
Neoplasia endocrina múltiple
Enfermedad de Alzheimer

Cerca de 6.000 enfermedades genéticas, de las cuales ya podemos diagnosticar unas 2.000,
(analizando genes individuales)



www.ncbi.nlm.nih.gov/omim

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NCBI

OMIM
Online Mendelian Inheritance in Man

Johns Hopkins University

All Databases | PubMed | Nucleotide | Protein | Genome | Structure

Entrez

OMIM
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Search Gene Map
Search Morbid Map

Help
OMIM Help
How to Link

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Numbering System
Symbols
How to Print
Citing OMIM
Download

OMIM Facts
Statistics
Update Log
Restrictions on Use

OMIM Statistics for November 8, 2010

Number of Entries

	Autosomal	X-Linked	Y-Linked	Mitochondrial	Total
* Gene with known sequence	12526	615	48	35	13224
+ Gene with known sequence and phenotype	345	19	0	2	366
# Phenotype description, molecular basis known	2627	233	4	28	2892
% Mendelian phenotype or locus, molecular basis unknown	1634	133	5	0	1772
Other, mainly phenotypes with suspected mendelian basis	1847	130	2	0	1979
Total	18979	1130	59	65	**20233**

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El diagnóstico genético

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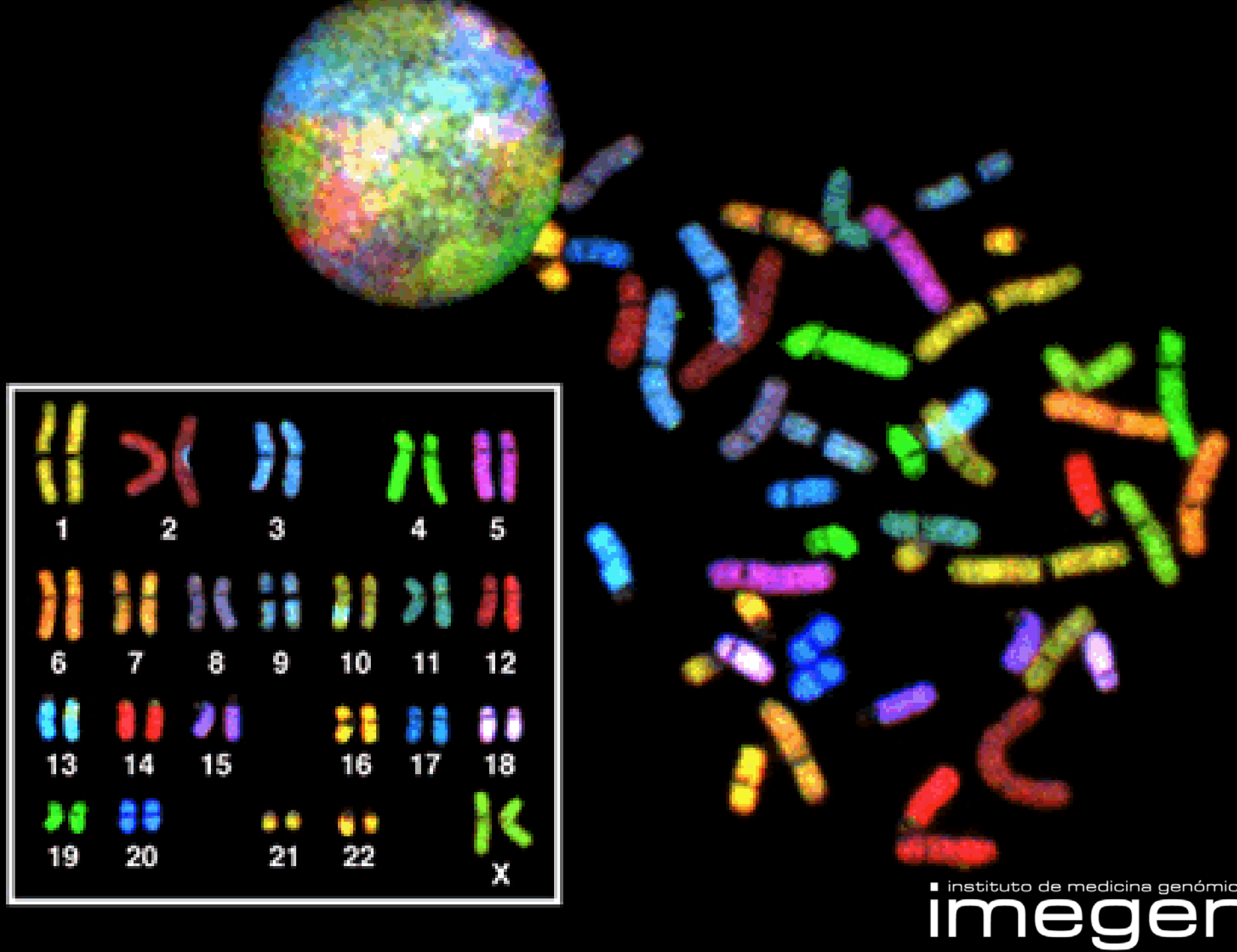

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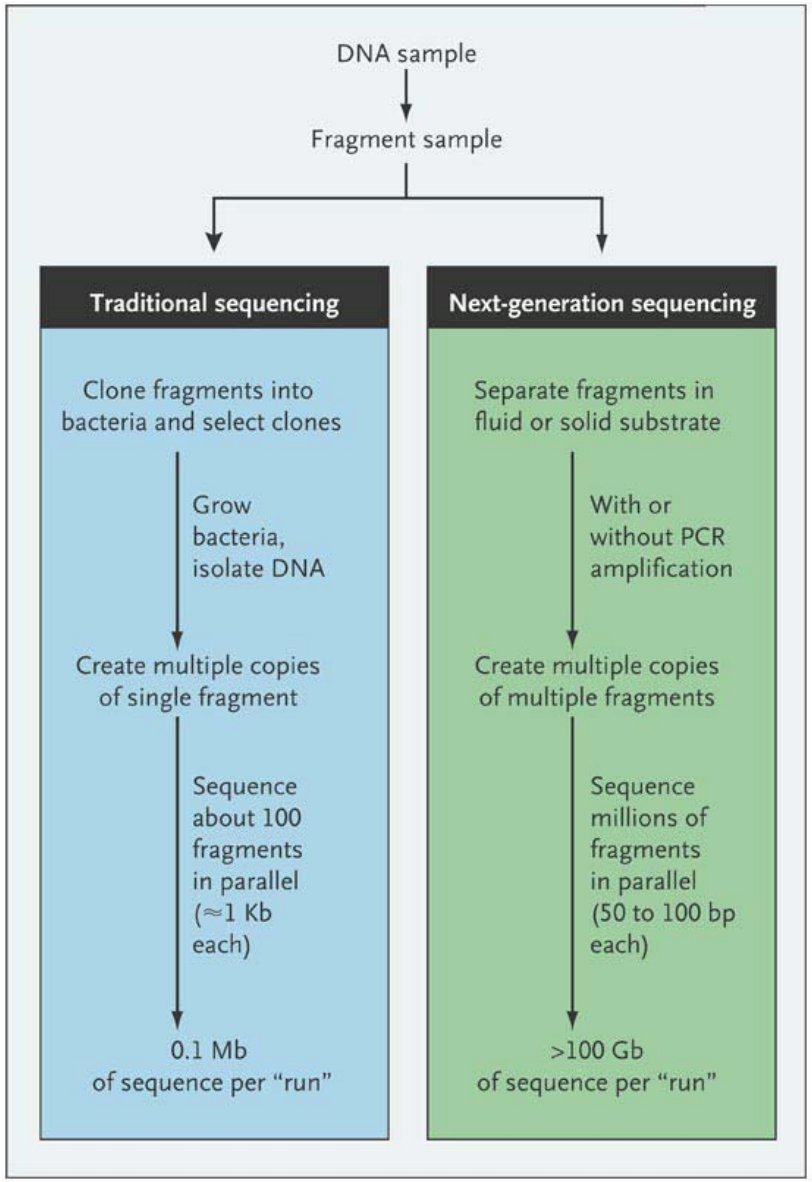
Técnicas para la secuenciación de ADN



Secuenciación capilar
(método de Sanger)
vs
Ultrasecuenciación

Feero et al (2010). N Engl J Med 362: 2001-2011.

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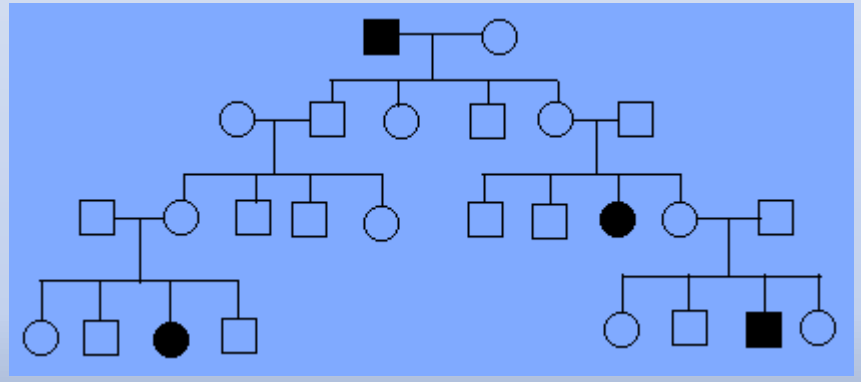
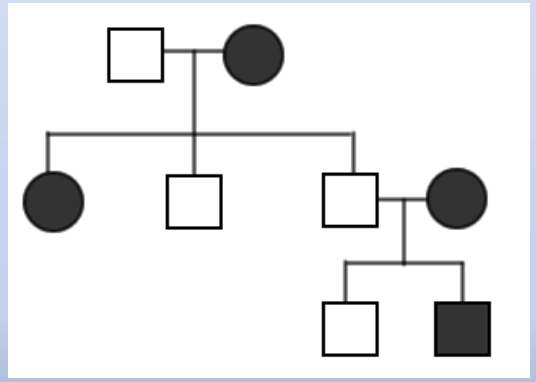
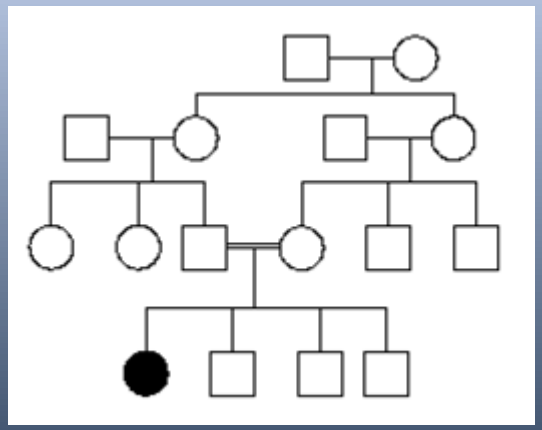
El proceso del diagnóstico genético

1. Consulta del paciente a su médico: valoración de antecedentes familiares.
2. Prescripción del análisis: toma de muestra.
3. Envío de la muestra al Laboratorio de Referencia.
4. Extracción de ADN genómico a partir de sangre del paciente.
5. Acceso a la región genómica relevante mediante amplificación por PCR.
6. Secuenciación del gen (o genes) relevante.
7. Comparación de la secuencia de ADN del paciente con las secuencias referencia y análisis bioinformático.
8. Comunicación de resultados.
9. Consejo genético antes y después del test .

Estudio de antecedentes familiares: árbol genealógico



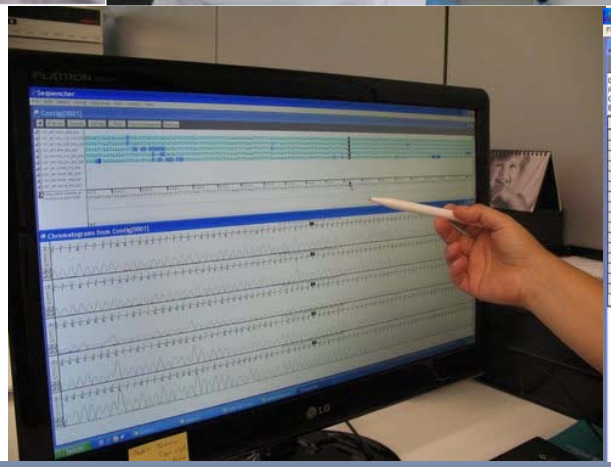
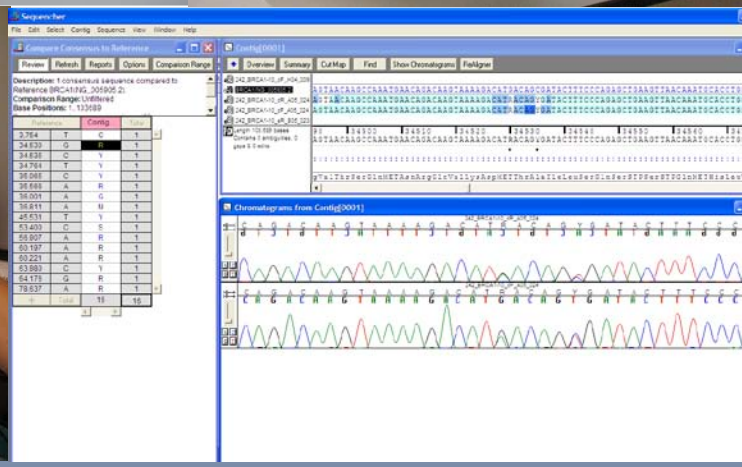




Acceso a la región relevante del genoma: PCR





Extracción y análisis del ADN

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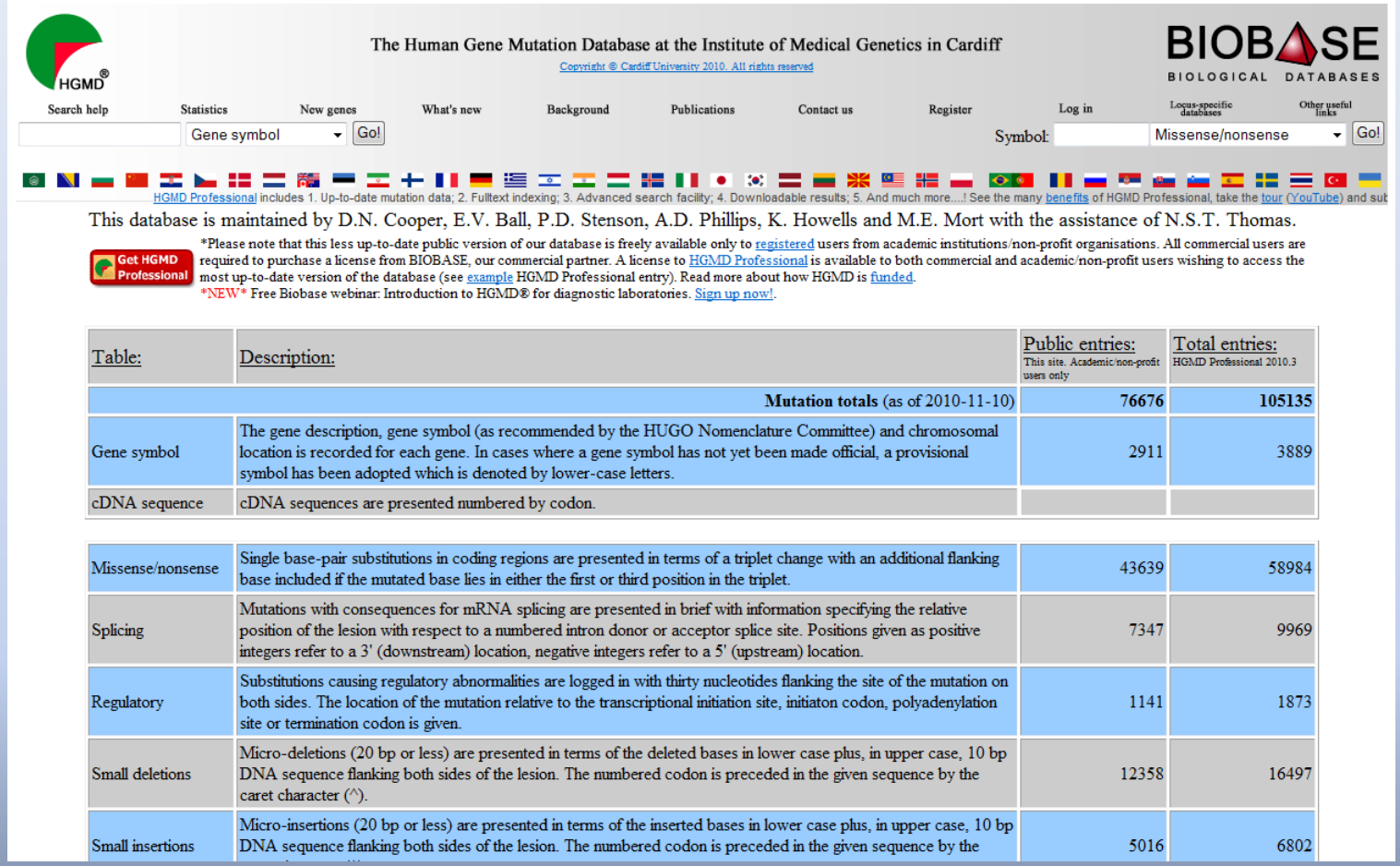

The Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff

HGMD® BIOBASE BIOLOGICAL DATABASES

Search help | Statistics | New genes | What's new | Background | Publications | Contact us | Register | Log in | Locus-specific databases | Other useful links

Gene symbol Go! Symbol: Missense/nonsense Go!

HGMD Professional includes 1. Up-to-date mutation data; 2. Fulltext indexing; 3. Advanced search facility; 4. Downloadable results; 5. And much more....! See the many benefits of HGMD Professional, take the tour (YouTube) and sub

This database is maintained by D.N. Cooper, E.V. Ball, P.D. Stenson, A.D. Phillips, K. Howells and M.E. Mort with the assistance of N.S.T. Thomas.

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Table:	Description:	Public entries: This site. Academic/non-profit users only	Total entries: HGMD Professional 2010.3
	Mutation totals (as of 2010-11-10)	**76676**	**105135**
Gene symbol	The gene description, gene symbol (as recommended by the HUGO Nomenclature Committee) and chromosomal location is recorded for each gene. In cases where a gene symbol has not yet been made official, a provisional symbol has been adopted which is denoted by lower-case letters.	2911	3889
cDNA sequence	cDNA sequences are presented numbered by codon.		
Missense/nonsense	Single base-pair substitutions in coding regions are presented in terms of a triplet change with an additional flanking base included if the mutated base lies in either the first or third position in the triplet.	43639	58984
Splicing	Mutations with consequences for mRNA splicing are presented in brief with information specifying the relative position of the lesion with respect to a numbered intron donor or acceptor splice site. Positions given as positive integers refer to a 3' (downstream) location, negative integers refer to a 5' (upstream) location.	7347	9969
Regulatory	Substitutions causing regulatory abnormalities are logged in with thirty nucleotides flanking the site of the mutation on both sides. The location of the mutation relative to the transcriptional initiation site, initiaton codon, polyadenylation site or termination codon is given.	1141	1873
Small deletions	Micro-deletions (20 bp or less) are presented in terms of the deleted bases in lower case plus, in upper case, 10 bp DNA sequence flanking both sides of the lesion. The numbered codon is preceded in the given sequence by the caret character (^).	12358	16497
Small insertions	Micro-insertions (20 bp or less) are presented in terms of the inserted bases in lower case plus, in upper case, 10 bp DNA sequence flanking both sides of the lesion. The numbered codon is preceded in the given sequence by the	5016	6802

Comparación frente a bases de datos de mutaciones

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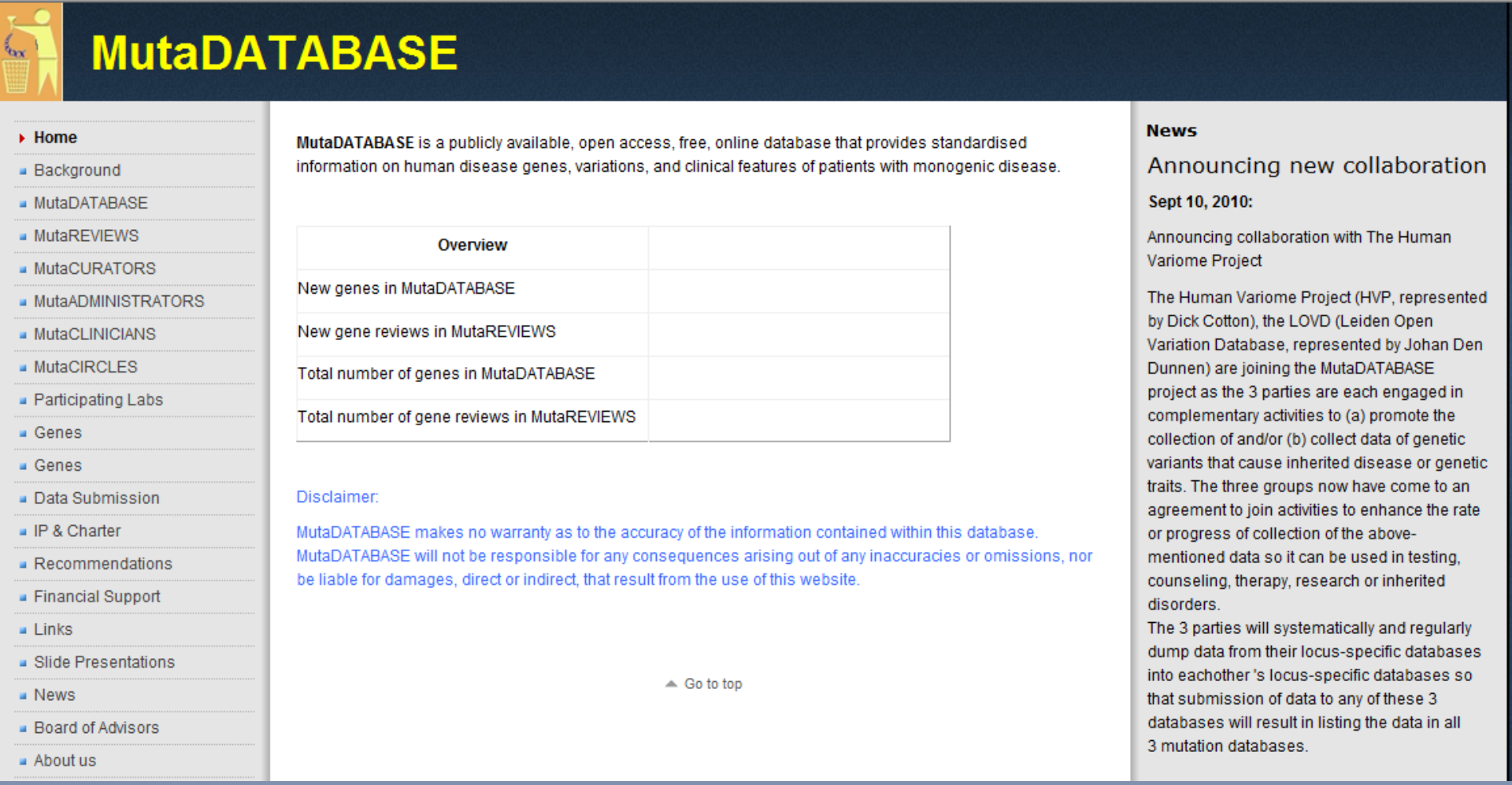

Iniciativas para unificar las bases de datos de mutaciones

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La Medicina Genómica y Medicina Personalizada

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Del análisis de genes individuales
al
análisis del genoma completo

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Perspective

JULY 22, 2010

The Path to Personalized Medicine

Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.

Major investments in basic science have created an opportunity for significant progress in clinical medicine. Researchers have discovered hundreds of genes that harbor variations contributing to human illness, identified genetic variability in patients' responses to dozens of treatments, and begun to target the molecular causes of some diseases. In addition, scientists are developing and using diagnostic tests based on genetics or other molecular mechanisms to better predict patients' responses to targeted therapy.

The challenge is to deliver the benefits of this work to patients. As the leaders of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA), we have a shared vision of personalized medicine and the scientific and regulatory structure needed to support its growth. Together, we have been focusing on the best ways to develop new therapies and optimize prescribing by steering patients to the right drug at the right dose at the right time.

We recognize that myriad obstacles must be overcome to achieve these goals. These include scientific challenges, such as determining which genetic markers have the most clinical significance, limiting the off-target effects of gene-based therapies, and conducting clinical studies to identify genetic variants that are correlated with a drug response. There are also policy challenges, such as finding a level of regulation for genetic tests that both protects patients and encourages innovation. To make progress, the NIH and the FDA will invest in advancing translational and regulatory science, better define regulatory pathways for coordinated approval of codeveloped diagnostics and therapeutics, develop risk-based approaches for appropriate review of diagnostics to more accurately assess their validity and clinical utility, and make information about tests readily available.

Moving from concept to clinical use requires basic, translational, and regulatory science. On the basic-science front, studies are identifying many genetic variations underlying the risks of both rare and common diseases. These newly discovered genes, proteins, and pathways can represent powerful new drug targets, but currently there is insufficient evidence of a downstream market to entice the private sector to explore most of them. To fill that void, the NIH and the FDA will

The new science of personalized medicine

The new science of personalized medicine:

Translating the promise into practice

PMC Personalized Medicine Coalition

The Case for

PERSONALIZED MEDICINE

We shed light on the demonstrated benefits of personalized medicine and describe the pathway for its widespread adoption to improve healthcare.

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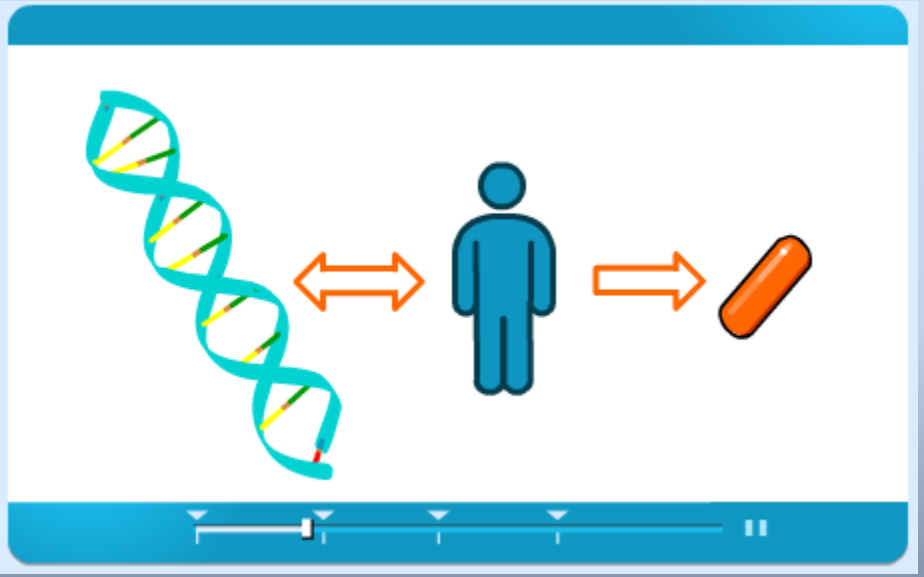
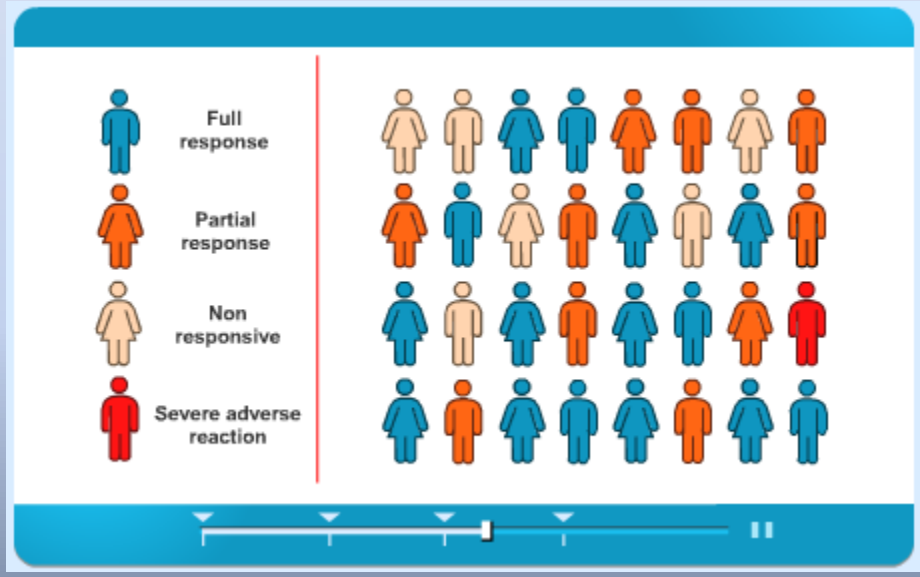
Aplicaciones de la Medicina Personalizada

- Farmacogenómica y farmacogenética
- Diagnóstico de la enfermedad y de la salud: medicina preventiva
- Genómica personal: tests genéticos directos al consumidor?

Farmacogenómica y farmacogenética





www.phgfoundation.org/tutorials/pharmacogenomics

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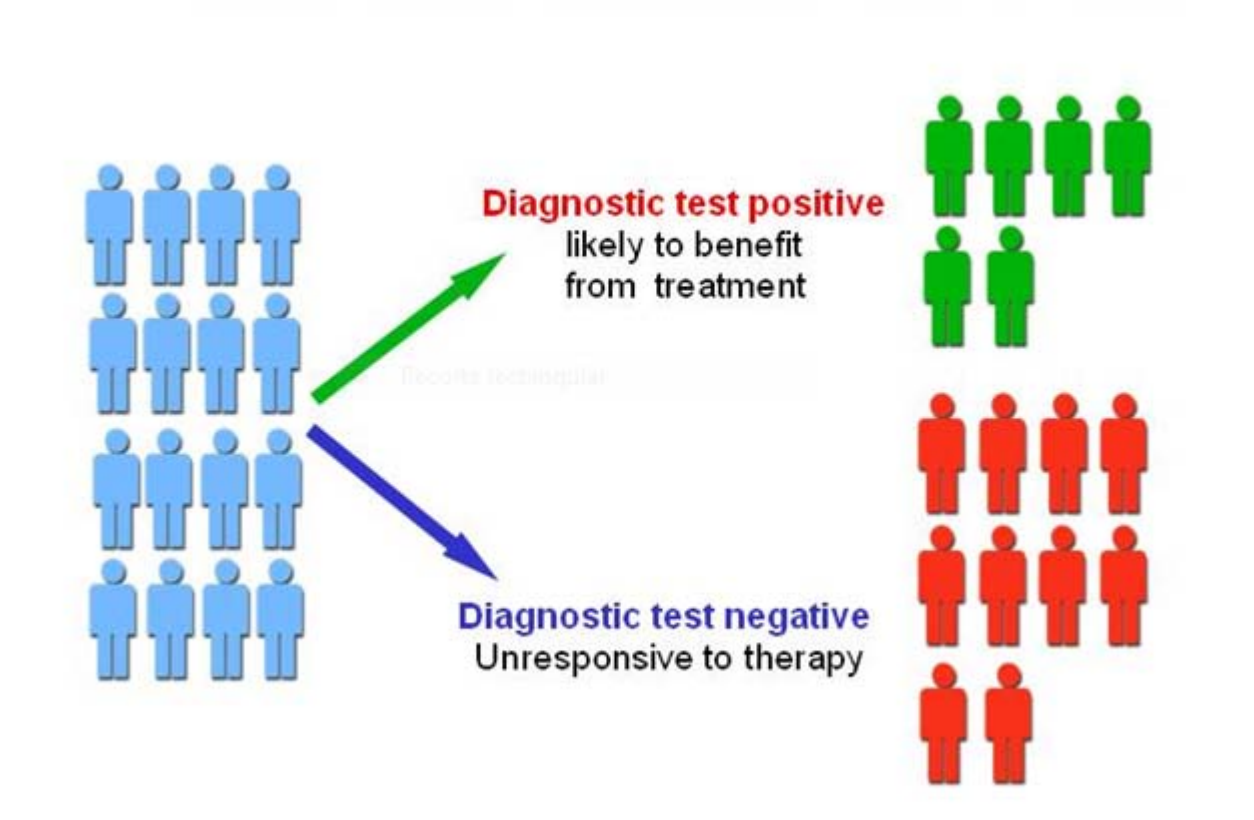

Science & Research (Drugs)
Research Areas
Genomics
- Pharmacogenomics Education Initiatives
- Genomics: FDA Staff Presentations
- Genomics: FDA Staff Publications
- Genomics: Upcoming and Past Events
- Additional Genomics-Related Resources

Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

Pharmacogenomic information is contained in about ten percent of labels for drugs approved by the FDA. A significant increase of labels containing such information has been observed over the last decade. In order to provide a reference for genomic biomarkers in labels of FDA-approved drug products, we created the table shown below. Genomic biomarkers can play an important role in identifying responders and non-responders, avoiding toxicity and adjusting the dosage of drugs to optimize their efficacy and safety. In the context of drug labels, these genomic biomarkers can be classified on the basis of their specific use, for example:

- Clinical response and differentiation,
- Risk identification,
- Dose selection guidance,
- Susceptibility, resistance and differential disease diagnosis,
- Polymorphic drug targets.

The table portrays a view on valid genomic biomarkers in the context of FDA-approved drug labels. It provides a comprehensive list of these markers and links to pharmacogenomic data, taking into account multiple regulatory contexts in which these biomarkers were approved. Most drug labels in this table provide pharmacogenomic information with no immediate recommendation for a specific action (i.e. genetic testing); however a few labels recommend or require genetic testing thereby specifying the use of these markers for reaching a therapeutic decision.

The table includes:

- Context-specific biomarker (column 1)
- Reference drug label information about the biomarker context within which the drug was approved (column 2 subsection 1)
- Prototypic drug associated with the label information defining the biomarker context (column 2 subsection 2)
- Other drugs in a similar context (column 3)

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